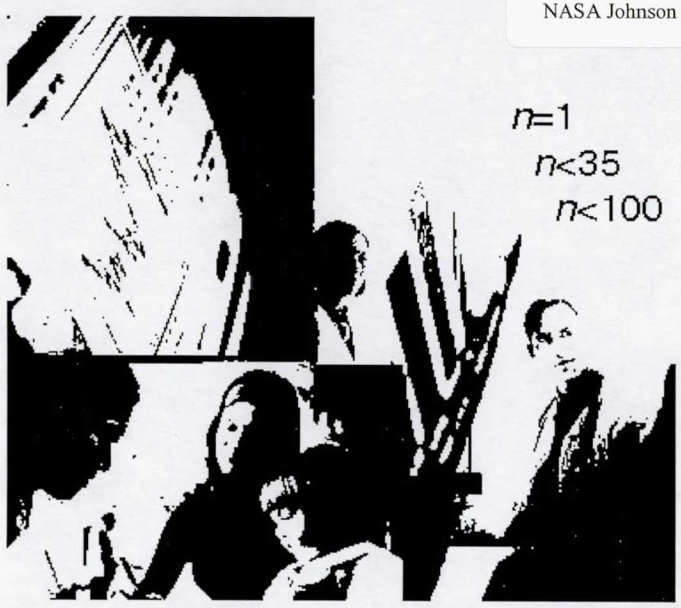
Future Directions for Small *n* Clinical Research Trials

A workshop being held by

The Committee on Strategies for Small Number Participant Clinical Research Trials

National Academy of Sciences Lecture Room

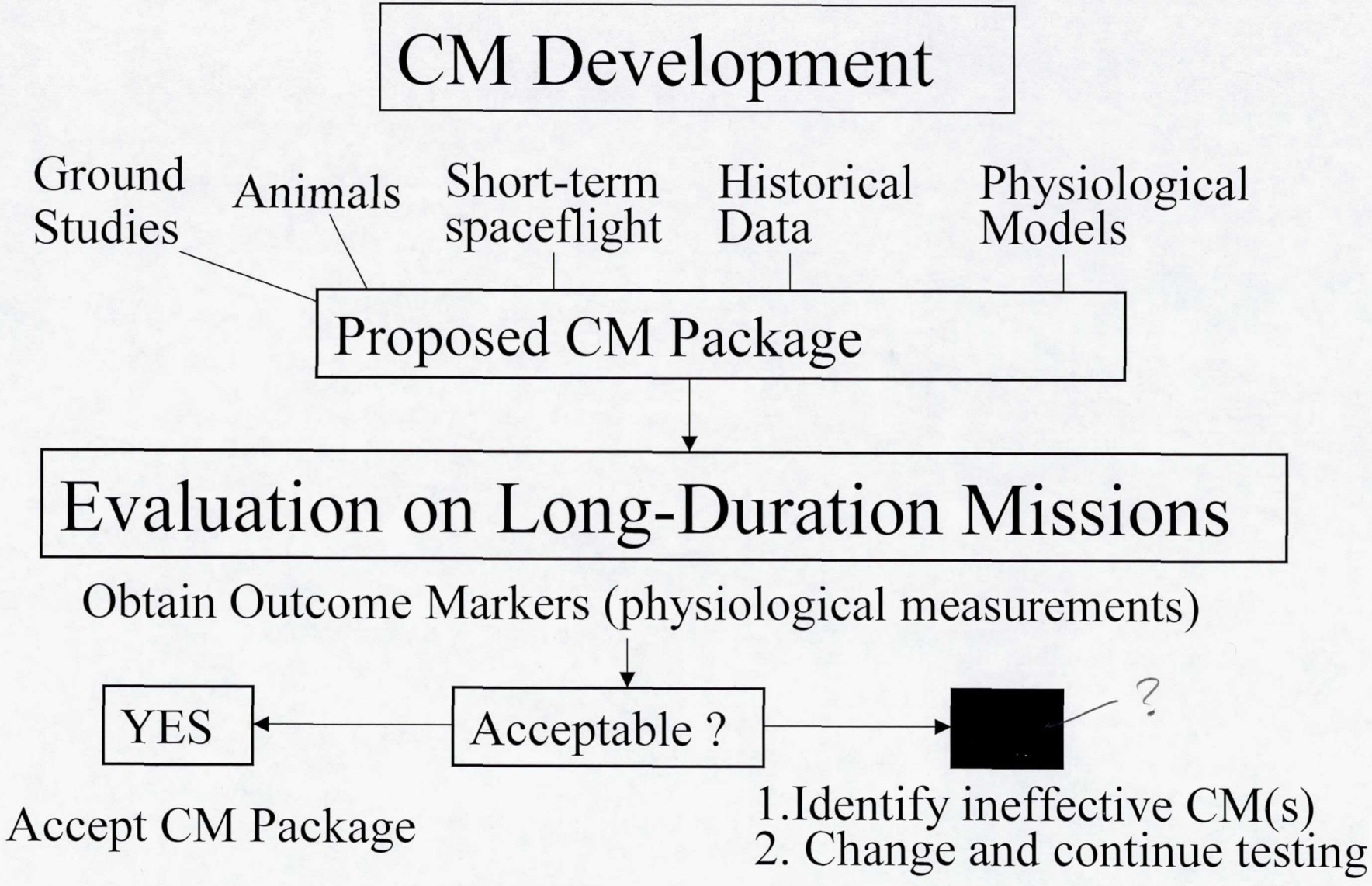
September 28, 2000



Quantitative Assessment of Countermeasure Efficacy for Long-Term Space Missions

Alan H.Feiveson – Medical Sciences Division

NASA Johnson Space Center


CM Development
Ground Studies
Animals
Short-term spaceflight
Historical Data
Physiological Models
Proposed CM Package
Evaluation on Long-Duration Missions
Obtain Outcome Markers (physiological measurements)
YES
Acceptable ?
?
Accept CM Package
1.Identify ineffective CM(s)
2. Change and continue testing

Definition of Performance Criteria

What are "acceptable" values
for outcome markers?

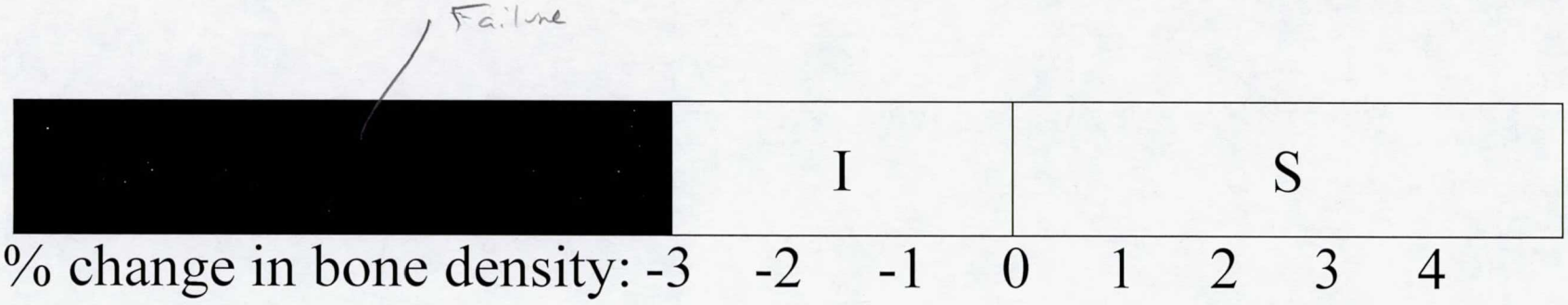
- Per subject-mission ("Level 1")
- Programmatic ("Level 2")
- Testability
- Operationally driven

Example: Bone Mineral Density (BMD)
Level 1 performance criteria for a bone region:

Outcome Marker: Bone Density

Performance Criteria:

- Success: Gain, or no loss relative to baseline.
- Failure: Severe loss (3% or more from baseline).
- Indeterminate: Small loss (less than 3% from baseline).



Quantitative Countermeasure Assessment Example
Level 2 performance criteria for a bone region:

Satisfactory performance:

Success (no bone loss) occurs on at least 90% of cases (astronaut-missions)

and

Failure (severe bone loss) occurs on no more than 5% of cases (astronaut-missions).

Unsatisfactory performance

Less than a 90% success rate *or* more than a 5% failure rate.

Quantitative Countermeasure Assessment (overview)

Definition of Performance Criteria for Physiological Systems

- Operationally driven
- Testability
- Per subject-mission
- Programmatic

ITR:Generate Outcome Markers

spell out

- Long missions
- Short missions
- Analog studies

Decision Process (sequential)

- Satisfactory performance - Accept current CM's protecting given physiological system
- Unsatisfactory performance - Identify ineffective CM's, then continue testing with remedies
- No decision – collect more data

Data Analysis

- Statistical properties of outcome markers
- Compliance assessment
- Meta analysis
- Uncertainty estimation
- Identification

Decision Process (no uncertainty)

Programmatic Specifications:

Success (no bone loss) on at least 90% of astronaut-missions
Failure (severe bone loss) on at most 5% of astronaut-missions

Actual Programmatic Parameters X and Y:

No bone loss on X% of astronaut-missions
Severe bone loss on Y% of astronaut-missions

Decision: (if X and Y assumed known)

$X \geq 90$ and $Y \leq 5$: Countermeasure package OK for bone.

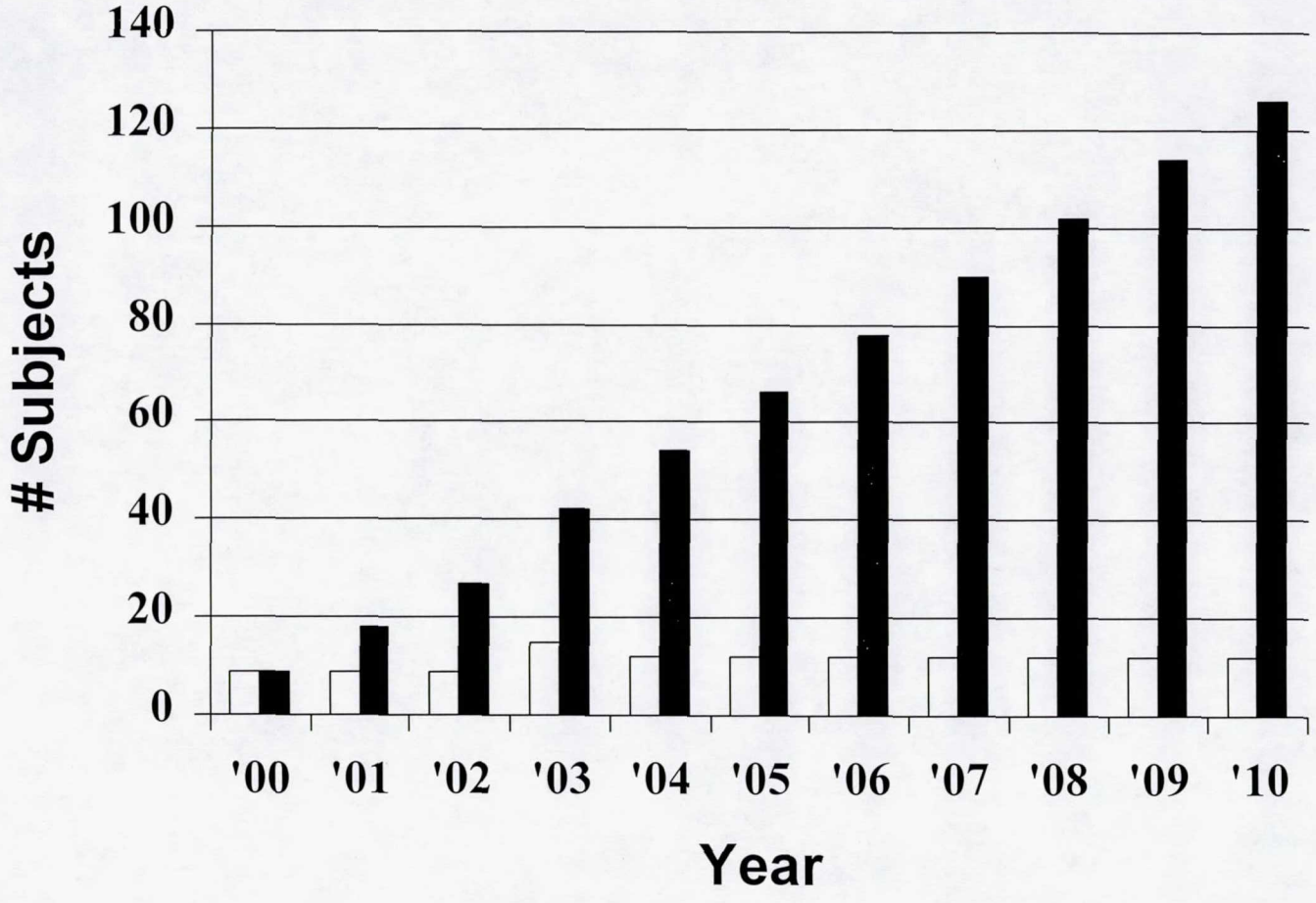
$X < 90$ or $Y > 5$: Bone CM not effective enough, take corrective action.

Sources of Uncertainty in the Decision Process

(Quantitative Countermeasure Assessment)

- Differences between individuals (sample size)
- Differences within individuals through time
- Variable degrees of countermeasure compliance
- Differences between missions
- Non-repeatability of ITR (procedural)
- Variation in time of application of ITR
- Direct measurement errors (output of ITR)

Long-Duration Crew Members Available for All Flight Research, Including CM Validation



Assumptions:
Full international participation
2000 - 2003
3 crew members/increment
3-5 month missions
2003 - 2010
6 crew members/increment
6 month missions

Decision Process (with uncertainty)

Programmatic Specifications:

Success (no bone loss) on at least 90% of astronaut-missions

Failure (severe bone loss) on at most 5% of astronaut-missions

Interval Estimates of Performance Parameters:

Gain or no bone loss occurs in (X1, X2) percent of cases

(X1, X2) = 90% confidence limits

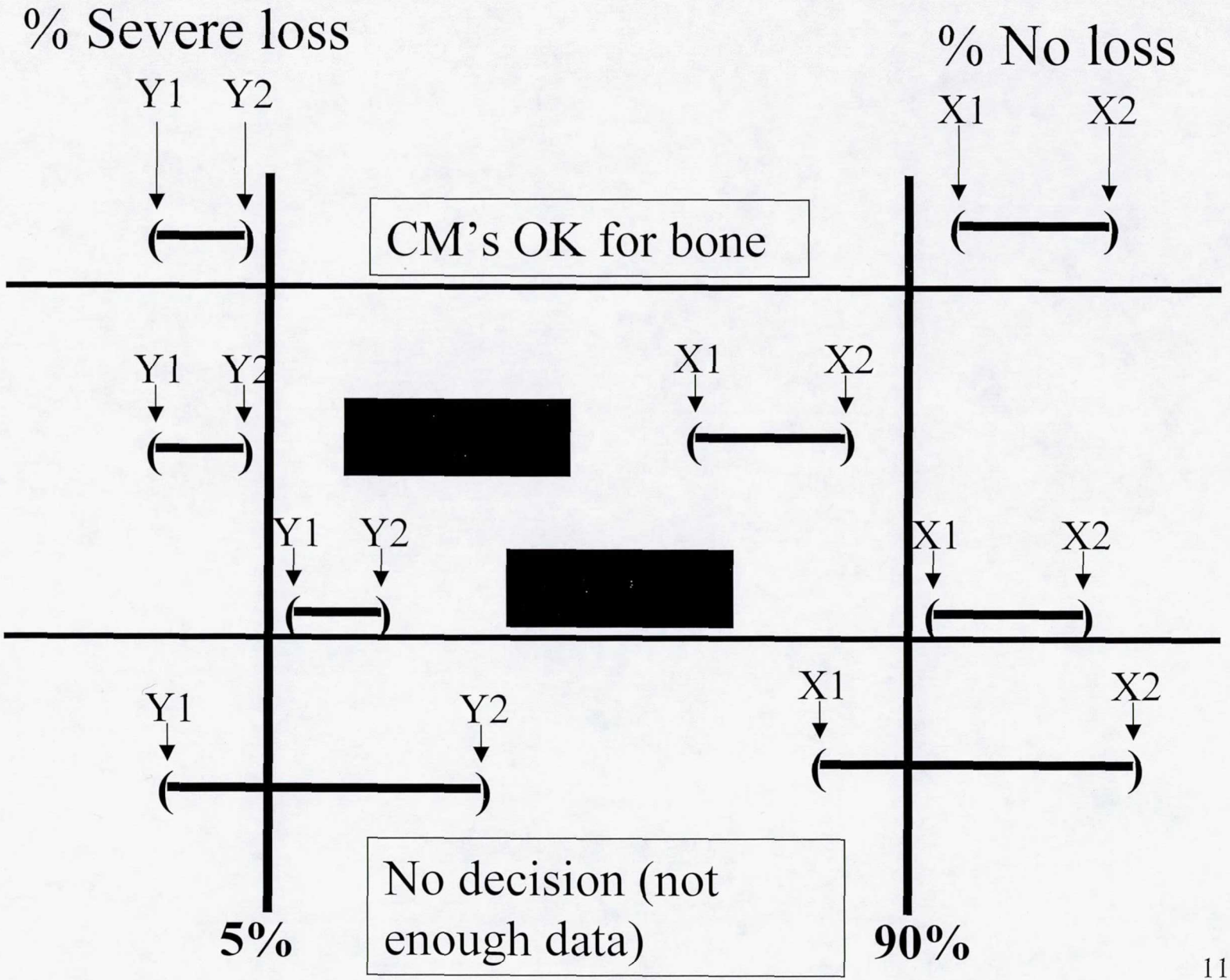
Severe bone loss (> 3%) occurs in (Y1, Y2) percent of cases

(Y1, Y2) = 90% confidence limits

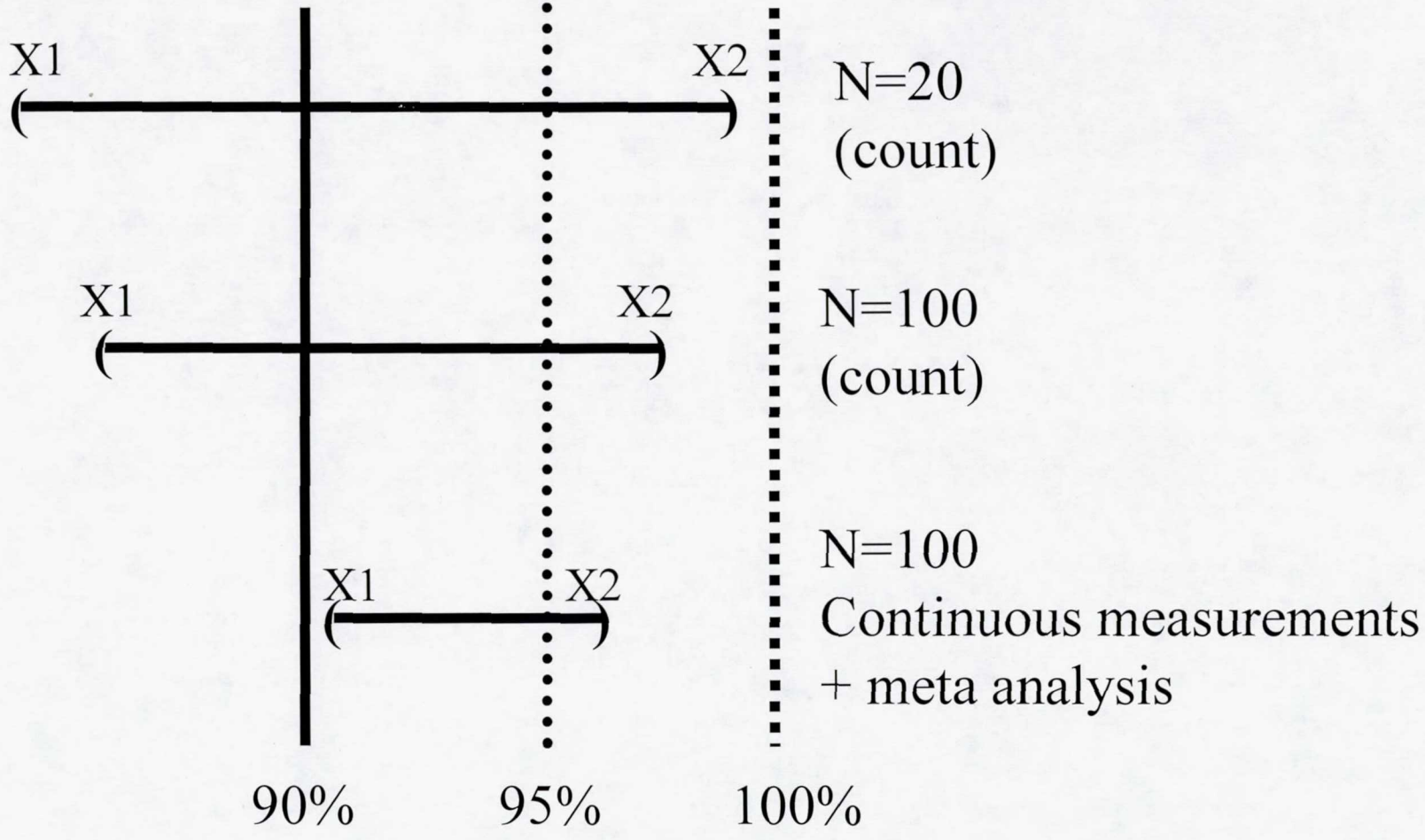
Decision:

- ☐ X1 $\geq$ 90 and Y2 $\leq$ 5: Countermeasure package OK for bone.
- ■ X2 < 90 or Y1 > 5: Bone CM not effective enough, take corrective action.
- ☐ Otherwise: Continue to use bone CM, collect more data

Decision Process (cont.)

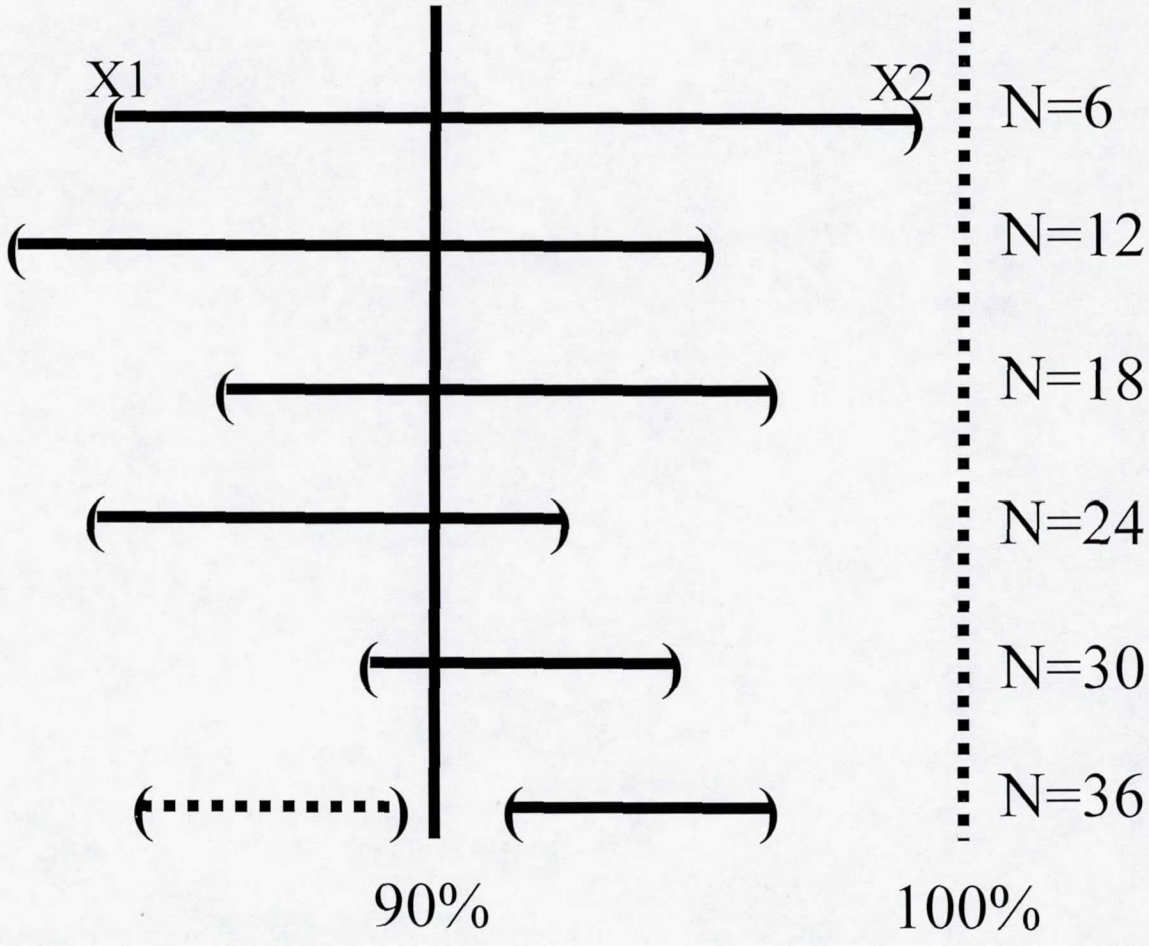


Width of confidence intervals depends on sample size and statistical properties of ITR measurements



Sequential decision process

Repeated confidence intervals for the system success rate



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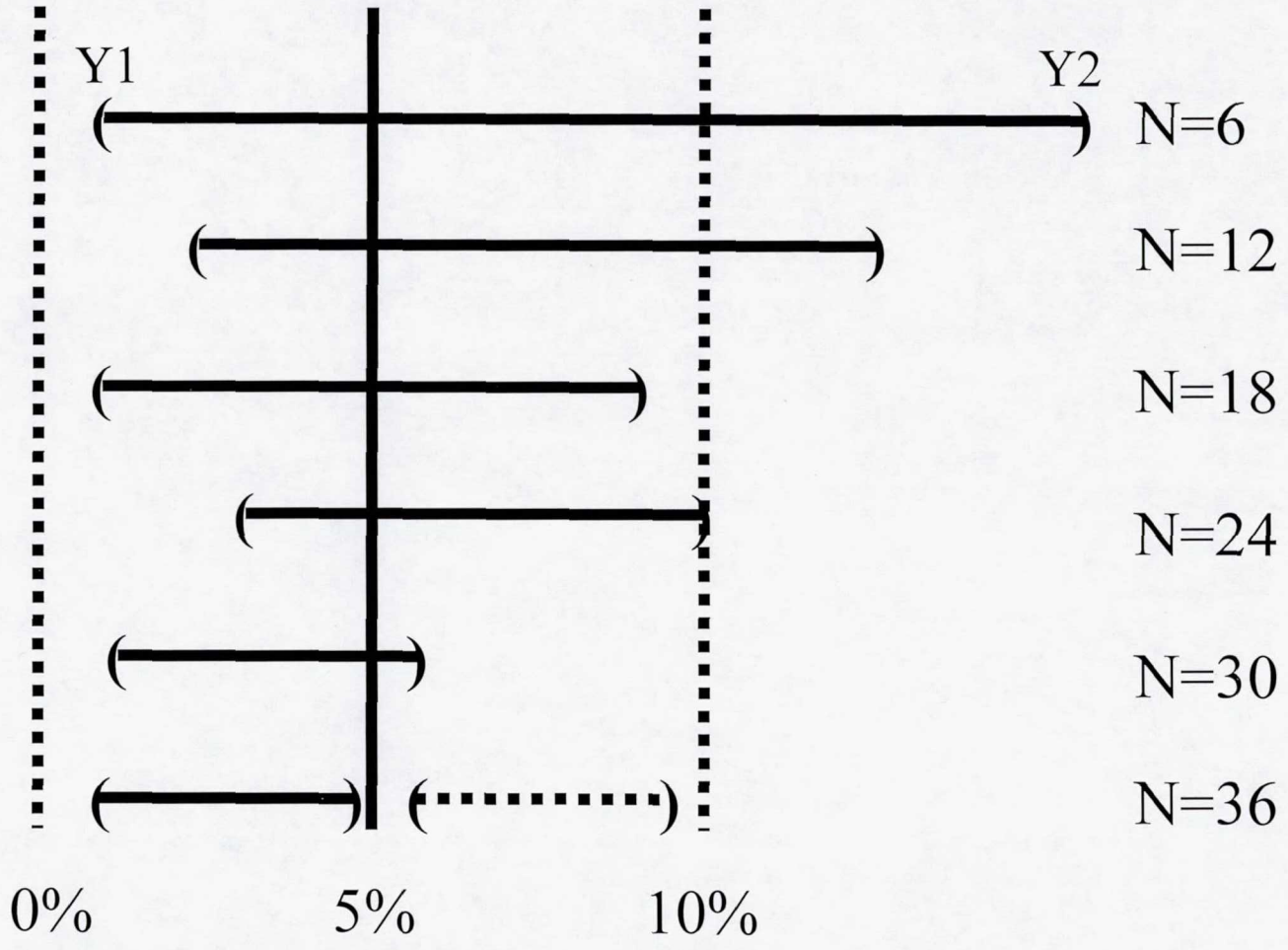

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